

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Fengxia Qi et al.

Application No.: 10/790,914

Confirmation No.: 1392

Filed: March 2, 2004

Art Unit: 1645

For: NOVEL LANTHIONINE ANTIBIOTIC
COMPOSITIONS AND METHODS

Examiner: V. L. Ford

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on April 2, 2007, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

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I. REAL PARTY IN INTEREST

The real party in interest for this appeal is The UAB Research Foundation, the assignee of the above-referenced application, the assignment having been recorded on August 2, 2005, Reel 016342, Frame 0099.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 9-28, all the claims pending in the application on which this appeal is based, stand finally rejected. Claims 9 and 10 stand rejected under 35 U.S.C. §102(b) as anticipated by Loyola-Rodriguez et al. (J. Gen. Microbiol., 138:269-274, 1992). Likewise, claims 9 and 10 stand rejected under 35 U.S.C. §102(b) as anticipated by Ikeda et al. (Infection and Immunity, 35:861-868, 1982). Claims 9 and 10 also stand rejected under 35 U.S.C. §102(b) as anticipated by Ooshima et al. (Microbiol. Immunol., 29:1163-1173, 1985). Lastly, claims 9-28 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

IV. STATUS OF AMENDMENTS

All amendments filed in this application have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a method for treating or preventing a gram-positive infection in a subject that includes the administration of a purified and isolated peptide with a

sequence as provided at SEQ ID No: 2. The subject protein is mutacin I structural protein having a molecular weight of approximately 2,364 Daltons and composed of 24 amino acids in mature form (page 9, lines 4-8). The recited pharmaceutically acceptable salt, amide, ester or prodrug of the same are taught (page 19, line 12 – page 21, line 16). Administration orally per claim 10 for oral prophylaxis in the form of a mouthwash, dentifrice or chewing-type gum is disclosed (page 13, lines 5-15). Oral ingestible forms of administration are also provided (page 13, line 16 – page 14, line 21). Topical administration per claim 11 is provided (page 16, lines 13-18). Application of the peptide to the surface of a medical device per claim 12 is provided (page 18, lines 13-22). The subject matter of dependent claims 13-16 pertaining to specific medical devices and processes for coating protein to medical devices are provided at page 18, line 13 – page 19, line 11. The only other independent claim pending, claim 17, is a narrower version of claim 9 as detailed above with a specific recitation of a Markush group of gram-positive bacterium. Teaching as to effectiveness against particular pathogens is provided at page 33, lines 10-13. The remaining dependent claims, claims 18-24, track pending claims 10-16 that are dependent from independent claim 9 and have been discussed above. Dependent claims 25-28 call out specific members of the Markush group of independent claim 17 and find like support in the specification at page 33, lines 10-13.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

As set forth in the final Office Action of Paper No. 20070303 mailed March 23, 2007, the grounds of rejection are anticipation of claims 9 and 10 by Loyola-Rodriguez et al. and separately by Ikeda et al., and separately by Ooshima et al., as well as rejection of all the pending claims 9-28 as failing to comply with the enablement requirement.

VII. ARGUMENT

A principal question raised on appeal as to prior art is whether an indeterminate teaching set forth in a prior art reference satisfies the requirements for anticipatory inherency. Appellant's answer to this question is no. (See *Rosco, Inc. v. Mirror Lite Co.*, 64 USPQ2d 1676 for controlling law as to inherency in support of Appellant's position.)

Loyola-Rodriguez et al. is cited for the teaching that "mutacin may be a candidate for use in dental caries prevention (see the Abstract). The amino acid sequence as set forth in SEQ ID NO: 2 [of the pending claims] would be inherent in the teachings of the prior art." (Paper No. 20070303, section 3, page 2). The basis of the rejection is that the Office lacks facilities to test, namely characterize the teaching of Loyola-Rodriguez et al. and that the smaller mutacin of the claimed methodology **MAY POSSIBLY BE PRESENT** within the larger protein of Loyola-Rodriguez et al. Appellant submits that this rejection improperly applies the doctrine of inherency to overcome apparent structural and source organism differences.

The law as to inherent anticipation is well established in requiring that the missing element absolutely must be present in the thing described in the reference and not merely probably or possibly present. In *Rosco Inc. v. Mirror Lite Co.*, 64 USPQ2d 1676, 1680, the court has stated:

Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element "is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599

(Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)).

Appellant believes that given the teachings of this reference, there is no basis for the assertion that the protein of SEQ ID No: 2 is necessarily present in the protein described by Loyola-Rodriguez et al.

In particular, although the Examiner states that “[t]he peptide used in the claimed method is isolated and purified from *Streptococcus mutans*...” and “[t]hese properties are taught by the peptide of the prior art” (Paper No. 20060801, section 4, page 4), Appellant notes that the polypeptide described in Loyola-Rodriguez et al. is isolated from *S. sobrinus*, not *S. mutans*. (Loyola-Rodriguez et al., Abstract).

The distinction between the source of MT6223 and currently claimed polypeptides has been previously made of record in the Declaration by Dr. Page Caufield which definitively states that MT6223, the polypeptide described in Loyola-Rodriguez et al., “is isolated from *Streptococcus sobrinus* while mutacin I is isolated from *Streptococcus mutans*.” A copy of the Declaration is provided at Appendix B.

Thus, Appellant submits that the protein disclosed in Loyola-Rodriguez, MT6223, is not identical to the protein of SEQ ID No: 2 based on the identification of these proteins as having different molecular weights, among other physical distinctions. Further, these two proteins are isolated from different species, not from the same source as asserted by the Examiner. Thus, it is submitted that there is no reasonable basis for the assertion that the protein of SEQ ID No: 2 is necessarily present in MT6223 as is required to reject a claim as anticipated based on inherency.

A secondary issue of the outstanding rejection is use of the transitory phrase “comprising” in pending independent claim 9 as somehow opening SEQ ID No: 2 to the

inclusion of effectively any protein. Appellant submits that this position is flawed for several reasons including pending claim 9 being a method claim and to place the current transitory phrase with a closed-ended transitory phrase would have the effect of closing method claim 9 to additional method steps as the transitory phrase of the method claim modifies the subsequent steps provided in the claim (see MPEP 2111.03 in support of Appellant's position). Additionally, even assuming for argument's sake that claim 9 was rendered as a composition claim, a properly anticipatory reference would nonetheless have to include at a minimum an amino acid sequence as provided in SEQ ID No: 2, or a salt, amide, ester or prodrug thereof. As detailed above, Appellant submits that there is no indication that a protein sequence of SEQ ID No: 2 is "necessarily present" in Loyola-Rodriguez et al.

As to the anticipatory rejections to be reviewed regarding the cited references Ikeda et al. and Ooshima et al., Appellant notes that these references both describe a protein isolated from *S. mutans* C3603. The Ikeda et al. article describes the protein as "bacteriocin C3603." (Abstract and throughout). The Ooshima et al. article refers to the Ikeda et al. article and states that "[b]acteriocin C3603 was isolated from the culture supernatant of *S. mutans* C3603 (serotype c) as described previously (7)" where (7) indicates reference to the Ikeda et al. article cited by the Examiner. (Ooshima et al., "Materials and Methods," first sentence and "References"). Thus, it is submitted that the two articles, Ikeda et al. and Ooshima et al., refer to the same protein "bacteriocin C3603."

Appellant submits that the protein bacteriocin C3603 is not equivalent to the protein of SEQ ID No: 2 described in the present specification and included in claims 9 and 10. For example, the molecular weight of bacteriocin C3603 is cited as 4800 Daltons (Ikeda et al.,

Abstract) which contrasts with the smaller size of the protein of SEQ ID No: 2 described in the present specification.

In addition, careful reading of these references shows that it is logically inconsistent to maintain that the protein bacteriocin C3603 could inherently “include” the protein of SEQ ID No: 2. Ikeda et al. includes the information that “...bacteriocin C3603 contains aspartic acid, threonine, serine, glutamic acid, glycine, alanine, valine, methionine, isoleucine, tyrosine, phenylalanine, tryptophan, lysine and arginine.” (Page 866, col. 1). In contrast, the present specification shows that the protein of SEQ ID No: 2 contains leucine, cysteine, asparagine and proline. Appellant submits that the protein of Ikeda et al. and Ooshima et al. could not “contain” the protein of SEQ ID No: 2 without also containing the amino acids leucine, cysteine, asparagine and proline.

In summary, in view of the clearly defined physical differences between the proteins described in the cited references and that of SEQ ID No: 2, as well as the differing sources of those proteins, Appellant submits that the Examiner has not established that any of the references describes a protein that necessarily includes the protein of SEQ ID No: 2 and therefore the references do not inherently disclose the protein of SEQ ID No: 2. Since it is well established that “[t]o anticipate a claim, the reference must teach every element of the claim” (MPEP 2131), Appellant submits that the references are not anticipatory directly or under the doctrine of inherency.

Appellant again reiterates with respect to the anticipatory rejections to be reviewed regarding Ikeda et al. and Ooshima et al. that reliance on the transitory phrase of method claim 9 being “comprising” as being a basis for satisfying the requirements of the proper anticipatory rejection under 35 U.S.C. §102(b) is misplaced.

The second principal question raised on appeal is whether a method of treatment is not enabled because the specification fails to enable every method indication. Appellant's answer to this question is no. (See MPEP 2164.01 in support of Appellant's position.)

The basis of the enablement rejection under review is failure to comply with the enablement requirement is that the claims are drawn to a method of treating or preventing all gram-positive bacterial infections.

Appellant notes that claims are enabled when one of skill in the art would know how to make and use the claimed invention without undue experimentation given the disclosures in the patent application coupled with information known in the art. MPEP 2164.01 It is submitted that the present claims are believed to meet this standard and are therefore enabled. Implicit in this rejection is the apparent enablement as to the gram-positive bacterial strains disclosed in the instant specification.

Appellant submits the Examiner's burden in rejecting claims as unenabled under 35 U.S.C. §112, first paragraph, as detailed in the Manual of Patent Examining Procedure Section 2164.04, includes, at a minimum, giving reasons for the uncertainty of the enablement. Specifically, this requires provision of "factors, reasons and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation..." (MPEP 2164.04). Still more specifically, this section suggests "specific findings of fact, supported by evidence, and then drawing conclusions based on these findings of fact."

Appellant submits that instead of meeting these requirements the enablement rejection under review is based on cited references which describe various pathogenic bacteria and noted that the present specification does not specifically include information regarding these bacteria.

As such, the enablement rejection under review lacks the required information showing that one of skill in the art would not know how to make and use the claimed invention with reference to any particular gram-positive organism.

Appellant notes the statements in the specification supporting the current claims to “a method of treating or preventing a gram-positive infection” (claim 9) and “a method of treating or preventing an infection in a subject, said method comprising administering to said subject infected with or susceptible to a gram-positive bacterium selected from the genus consisting of *Staphylococcus*, *Enterococcus*, and *Streptococcus pneumoniae*” (claim 17). For example, the specification states that mutacin I has advantages compared to conventional antimicrobial agents including that “it has a wide spectrum of antimicrobial activity against a wide range of gram-positive bacteria including the multidrug resistant *Staphylococci* and *Enterococci*...” (page 18, lines 1-4). The specification also states that “mutacin III is more potent than mutacin I against *Staphylococcus aureus* and *Staphylococcus epidermidis*, while both mutacins have equal activities against other pathogens such as enterococci, pneumococci, and Group A streptococci” (page 33, lines 10-13).

Appellant has made of record the Declaration by an inventor, Dr. Page Caufield (Appendix B), including data showing particular gram-positive organisms’ response to the action of mutacin I and supporting the disclosure of a wide spectrum of antimicrobial activity against a wide range of gram-positive bacteria including the multidrug resistant *Staphylococci* and *Enterococci*. The Declaration includes data and description of effectiveness of mutacin I inhibition against various gram-positive organisms along with information indicating that “[b]ased on the broad spectrum of mutacin I to inhibit pathogenic gram-positive bacteria, I believe that one [of my colleagues] of skill in the field would have little difficulty in using or

testing the efficacy of mutacin I against a Gram positive bacterial target....” (Declaration, section 5). Appellant submits that the Declaration supports the assertion that undue experimentation is not required to make and use the methods of the present claims.

In addition, Appellant submits that testing the susceptibility of a particular microorganism to an inventive peptide is well within the talents of one of skill in the art as evidenced by published results. In support of this position, Appellant refers to the Loyola-Rodriguez reference for an exemplary teaching with respect to Table 2 of methodologies for measuring the level of success.

Further, testing the activity of even well-known antibiotic compositions on a lab sample from a patient is submitted to be a routine part of medical practice. In support of this position, Appellant has made of record to meet the 35 U.S.C. §112, first paragraph, requirement an article supporting this assertion entitled “Agar Plate Dilution Method for Routine Antibiotic Susceptibility Testing in a Hospital Laboratory” (A. J. Clinical Pathol., 60:384-394, 1973) (see Appendix B).

Thus, Appellant contends that the disclosure provides adequate guidance and that any experimentation necessary would be routine and not undue experimentation. It is therefore submitted that the current claims are enabled since one of ordinary skill in the art would be able to make and use the invention without undue experimentation.

For all the foregoing reasons, Appellant respectfully submits that the outstanding rejections of claims 9-28 are in error and should be reversed. Such action is respectfully solicited.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include all the amendments filed by Appellant.

Dated: 5-2-07

Respectfully submitted,

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APPENDIX A

9. A method of treating or preventing a gram-positive infection in a subject, said method comprising administering to said subject an effective amount of a purified and isolated peptide having the amino acid sequence as set forth in SEQ ID No: 2, or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof.

10. A method according to claim 9, wherein the peptide is administered orally.

11. A method according to claim 9, wherein the peptide is administered topically.

12. A method according to claim 9, wherein the peptide is applied to a surface of a medical device.

13. A method according to claim 12, wherein the medical device is a catheter.

14. A method according to claim 12, further including the step of coating the medical device with the peptide prior to contacting the subject therewith.

15. A method according to claim 12 wherein said medical device is selected from the group consisting of: a tube, artificial valve, a pacemaker and an implantable device.

16. A method according to claim 12 further including the step of linking the peptide to a polymer prior to being applied to the surface of the medical device.

17. A method of treating or preventing an infection in a subject, said method comprising administering to said subject infected with or susceptible to a gram-positive bacterium selected from the genus consisting of *Staphylococcus*, *Enterococcus*, and *Streptococcus pneumoniae* an effective amount of a purified and isolated peptide having the amino acid sequence as set forth in SEQ ID No: 2, or a pharmaceutically acceptable salt, amide, ester, or prodrug thereof.

18. A method according to claim 17, wherein the peptide is administered orally.

19. A method according to claim 17, wherein the peptide is administered topically.

20. A method according to claim 17, wherein the peptide is applied to a surface of a medical device.

21. A method according to claim 20, wherein the medical device is a catheter.

22. A method according to claim 20, further including the step of coating the medical device with the peptide prior to contacting the subject therewith.

23. A method according to claim 20 wherein said medical device is selected from the group consisting of: a tube, artificial valve, a pacemaker and an implantable device.

24. A method according to claim 20 further including the step of linking the peptide to a polymer prior to being applied to the surface of the medical device.

25. A method according to claim 17 wherein the gram-positive bacterium is multi-drug resistant.

26. A method according to claim 17 wherein the gram-positive bacterium is a Group A Streptococcus.

27. A method according to claim 17 wherein the gram-positive bacterium is an Enterococcus.

28. A method according to claim 17 wherein the gram-positive bacterium is a Streptococcus pneumoniae.

APPENDIX B

Evidence has been entered under §1.132, namely the sworn Declaration of Paige Caufield ascribed to on January 17, 2006 and inclusive of an Appendix. Additionally, in support of enablement, a prior art article already of record entitled “Agar Plate Dilution Method for Routine Antibiotic Susceptibility Testing in a Hospital Laboratory” (A. J. Clinical Pathol., 60:384-394, 1973) is provided. No evidence pursuant to §§1.130 or 1.131 entered by or relied upon by the examiner is being submitted.

APPENDIX C

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.